REMARKS/ARGUMENTS

Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 are under consideration in the instant application.

Claims 26, 27, 58 and 59 have been amended.

Rejections Under 35 U.S.C. §112

The Examiner has rejected claims 26-32, 34, 36-42, 44, 46, 47, 49, 58 and 59 under 35 U.S.C, 112, first paragraph, as failing to comply with the written description requirement, as no support is provided for formulations in which lansoprazole is the sole ingredient. Applicant respectfully traverses the rejections of the Examiner by noting that lansoprazole is the only pharmaceutically active ingredient taught in the application and that all formulations feature only lansoprazole as the sole pharmaceutically active ingredient. Claims 26, 27, 58 and 59 have been amended to recite lansoprazole as the sole "pharmaceutically active ingredient".

Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 26-32, 34, 36-40, 42, 44, 46, 47, 49, 50, 58 and 59 under 35 U.S.C, 103, first paragraph, as being unpatentable over Depui et al (WO 96/24375) in view of Lundberg (EP 1174136) and Edgren et al. (US 6,210,712).

The Examiner states that WO '375 discloses an oral, enteric coated dosage form comprising an acid labile proton pump inhibitor useful in the treatment of disorders associated with *Heliobacter* infections (abstract). In Examples 5 (beginning of page 28) and 12 (beginning on page 39), a multilayer dosage form comprising lansoprazole (in the free base form) is prepared. The core contains a sugar sphere seed coated with lansoprazole, HPMC and water. No alkaline material is present in the core. The separating layer comprises HPHC, talc as filler, magnesium stearate, and water as the solvent. An enteric coating layer comprising a methacrylic acid and the plasticizer triethyl citrate is present in the dosage form. The active ingredient can be mixed with other ingredients such as binders, surfactants and fillers. In Example 18, the surfactant

sodium lauryl sulfate and the filler anhydrous lactose are included in the same layer as the active ingredient (omeprazole).

WO '375 does not disclose the use of sodium stearate or a surfactant such polysorbate 80 or sodium lauryl sulfate in the subcoating layer.

The Examiner states that Lundberg et al. discloses similar trilayer (active ingredient core, intermediate layer and enteric layer). In Example 1, a separating layer comprises talc (filler), sodium dodecyl sulfate (surfactant), microcrystalline cellulose (cellulosic polymer) and magnesium stearate (alkaline agent) is added. These ingredients are mixed with granulated active ingredient and no solvent is present. Disclosed pharmaceutically acceptable surfactants include non-ionic and ionic surfactants such as sodium lauryl sulfate or polysorbates.

Lundberg teaches a formulation in which an alkaline reacting compound is present in the core, and the separating layer is formed in situ during the enteric coating as a salt between the enteric coating polymer(s) and an alkaline reacting compound(s) in the core material. The separating layer comprises a water soluble salt of an enteric coating polymer.

Magnesium stearate, as taught in Example 1 of the prior art, is not present in the separating layer, but rather is mixed with dried granules comprising the active ingredient, which are then compressed into tablets prior to coating with an enteric coating dispersion in a single coating step. The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer, and does not comprise magnesium stearate.

The Examiner further states that Edgren et al discloses potassium stearate, magnesium stearate and sodium stearate as pharmaceutically acceptable lubricants.

According to the Examiner, the person of ordinary skill in the art would have been motivated to use sodium stearate because WO '375 teaches that magnesium stearate can be used in subcoating layer and Edgren et al discloses that magnesium stearate and sodium stearate are functionally equivalent as they are both lubricants.

The Examiner therefore considers that it would have been obvious to one of ordinary skill in the art to prepare a multi-layer dosage form as disclosed by WO '375 and to use sodium stearate and a surfactant in the subcoating layer.

No hint or suggestion is provided by Edgren that any of the stearates disclosed as possible lubricants are suitable for use as an alkaline agent in a pharmaceutical composition, let alone in a subcoating layer.

As disclosed in column 4, last paragraph, the dosage form disclosed by Edgren comprises a first coat (16) comprising 100 wt% ethylcellulose, or a blend of ethylcellulose and hydroxypropylcellulose giving a total of 100 wt % of the first coating layer; a second coat (12) and an internal compartment (15). A push layer (22), comprising expandable osmopolymers, is further provided, for pushing the drug from the dosage form. The purpose of this push-layer is entirely different from the subcoating layer of the present invention, which, serves to provide a stable composition for oral administration of acid-labile substances.

As stated by the Examiner, Edgren (column 8, lines 6-10) discloses that potassium stearate, magnesium stearate and sodium stearate are pharmaceutically acceptable lubricants; however this section refers to the inclusion of lubricants in the push-layer, and not in the subcoating layer i.e. the layer over which an enteric coating is layered, as taught by the present invention. Thus, Edgren does not teach the use of magnesium stearate in the subcoating layer.

Hence, none of the cited prior art documents teaches the use of magnesium stearate in a subcoating layer, over which an enteric coating is layered. There would therefore be no motivation for one skilled in the art to include any stearate in a subcoating layer, let alone to use such a stearate as an alkaline agent. Furthermore, one of ordinary skill in the art would not select a reactive ingredient (an alkaline agent, which raises the pH of a solution) on the basis of its role as a non-reactive ingredient (a lubricant, which by definition should not be reactive with other ingredients).

Furthermore, Applicant maintains the previous assertion that magnesium stearate and sodium stearate are not functionally equivalent as alkaline agents. In order to act as an alkaline agent, a substance must be soluble in water to affect pH of a coating layer.

Magnesium stearate is not soluble in water while sodium stearate is soluble in water. Support for this position can be found in the USP (attached in a co-filed IDS). Furthermore sodium stearate is not acting as a lubricant in the presently claimed formulation.

The Applicant has previously stated that an alkaline agent is, by definition, soluble in water, hence insoluble magnesium stearate cannot be considered an alkali agent. In contrast, the formulation of the present invention uses soluble sodium stearate in the subcoating layer, which is effective as an alkalinizing agent. If the Examiner has any reference proving the contrary, in contrast to the USP definition provided with the co-filed IDS, the Examiner is respectfully requested to provide this reference.

According to the Webster online dictionary, an alkali is defined as 'any of various water-soluble compounds capable of turning litmus blue and reacting with an acid to form a salt and water'. A printed copy of the relevant webpage is also provided with the co-filed IDS. Thus, clearly magnesium stearate cannot be effective as an alkalizing agent; furthermore, none of the references cited by the Examiner or available to Applicant teach or suggest that in fact magnesium stearate could be effective as an alkalizing agent.

The Applicant therefore believes that claims 26-32, 34, 36-40, 42, 44, 46, 47, 49, 50, 58 and 59 are not rendered obvious by the teachings of WO'375 in view of Lundberg et al and Edgren et al.

The Examiner has further rejected claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 under U.S.C. 103(a) as being unpatentable over Depui WO '375, Lundberg and Edgren et al as applied above, and further in view of Napper et al (US 2002/0150618). The Examiner states that Napper et al discloses that either lactose monohydrate or anhydrous lactose are suitable directly compressible pharamaceutically acceptable excipients. Since, as discussed above, the Applicant contends that Depui, Lundberg and Edgren, either alone or in combination, fail to teach the use of a formulation comprising an alkaline agent in a subcoating layer, the use of either lactose monohydrate or anhydrous lactose with the compositions of the prior art would not result in the composition of the present invention.

The Examiner has further rejected claims 26-32, 34, 36, 38-42, 44, 46, 47, 49, 50, 58 and 58 under 35 U.S.C. 103(a) as being unpatentable over Depui et al (US 2002/0155153) in view of Lundberg and Edgren et al.

The Examiner states that Example 4 of Depui '153 teaches dosage forms comprising non-pareil cores coated with water, surfactant sodium lauryl sufate, lansoprazole and the cellulosic polymer HPMC. A separating (subcoating) layer comprised of water and ethanol as solvents, the filler talc, the surfactant PEG 6000 and the cellulosic polymer HPMC is applied. Then an enteric coating of HPMP, plasticizers acetyltributyl citrate and cetanol is applied. The separating barrier may serve as a diffusion barrier and pH buffering zone. Depui '153 does not disclose a lansoprazle preparation in which an inorganic or organic basic salt is present in the separating layer.

The Examiner states that Lundberg et al discloses similar trilayer dosage form wherein magnesium stearate is added to the separating layer, and that Edgren et al discloses potassium stearate, magnesium stearate and sodium stearate as being functionally equivalent. As discussed above, Lundberg does not disclose the use of magnesium stearate in the separating layer, and does not disclose that magnesium stearate functions as an alkaline agent. Further, Edgren does not disclose that these stearates are functionally equivalent as alkaline agents, but rather as lubricants, as described above (along with Applicant's further arguments in this regard).

The Examiner has further rejected claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 under U.S.C. 103(a) as being unpatentable over Depui '153, Lundberg and Edgren '153.

Depui '153, Lundberg and Napper teaches a lansoprazole dosage form with an active substrate center that does not contain an alkaline substance; a subcoating layer containing sodium stearate, a cellulosic polymer such as HPMC, a filler, polysorbate 80 or sodium lauryl sulfate as the surfactant and a solvent; and an enteric coating. None of the references disclose the use of lactose as filler material in the layer with the lansoprazole. WO '375 discloses that anhydrous lactose can be present in the core material of multi-layered benzimidazole proton pump inhibitor dosage. Napper discloses

that either lactose monohydrate or anhydrous lactose are suitable directly compressible pharmaceutically acceptable excipients.

As discussed above, since none of the cited references, either singly or in combination, disclose the use of a stearate as an alkaline agent in the subcoating layer, the use of lactose as filler material in combination with the compositions of the prior art would not result in the formulation of the present invention.

The present response is intended to be fully responsive to all points of objection raised by the Examiner and is believed to place claims 26-32, 34, 36-40, 42, 44, 46, 47, 49, 50, 58 and 59 in condition for allowance. Favorable reconsideration and allowance of the Application is respectfully requested.

CONCLUSION

Applicant believes that the claims are in condition for allowance. If the Examiner believes that a telephonic interview with the undersigned would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned at (301) 952-1011. Please charge any fees associated with this paper to deposit account No. 50-4801.

Respectfully submitted,

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